European Journal of Radiology 93 (2017) 100–106

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Research papers

Comparative study of post-transplant outcomes in hepatocellular carcinoma patients treated with chemoembolization or radioembolization

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ARTICLE INFO

Keywords:
Transarterial chemoembolization
Radioembolization
Liver transplantation
Downstaging

ABSTRACT

Purpose: To analyze long-term outcomes in patients bridged/downstaged to orthotopic liver transplantation (OLT) by transarterial chemoembolization (TACE) or yttrium-90 radioembolization (Y90) for hepatocellular carcinoma (HCC).

Methods: 172 HCC patients who underwent OLT after being treated with transarterial liver-directed therapies (LDTs) (Y90: 93; TACE: 79) were identified. Pre-LDT and pre-OLT clinical/imaging/laboratory characteristics including United Network for Organ Sharing (UNOS) staging and alpha-fetoprotein values (AFP) were tabulated. Post-OLT HCC recurrence was assessed by imaging follow-up per standard of care. Recurrence-free (RFS) and overall survival (OS) were calculated. Uni/multivariate and sub-stratification analyses were performed.

Results: Time-to-OLT was longer in the Y90 group (Y90: 6.5 months; TACE: 4.8 months; $p = 0.02$). With a median post-OLT follow-up of 26.1 months (IQR: 11.1–49.7), tumor recurrence was found in 6/79 (8%) TACE and 8/93 (9%) Y90 patients. Time-to-recurrence was 26.6 (CI: 7.0–49.5) and 15.9 months (CI: 7.8–46.8) for TACE and Y90, respectively ($p = 0.48$). RFS (Y90: 79 months; TACE: 77 months; $p = 0.84$) and OS (Y90: 57% alive at 100 months; TACE: 84.2 months; $p = 0.57$) were similar. 54/155 patients (Y90: 29; TACE: 25) were downstaged to UNOS T2 or less. RFS hazard ratios for patients downstaged to ≤T2 versus those that were not were 0.6 (CI: 0.33–1.1) and 1.7 (CI: 0.9–3.1) respectively ($p = 0.13$). 17/155 patients (Y90: 8; TACE: 9) that were > T2 were downstaged to UNOS T2 or less (within transplant criteria). Distribution (unilobar/bilobar), AFP, and pre-transplant UNOS stage affected RFS on univariate analyses.

Conclusion: Despite longer time-to-OLT for Y90 patients, post-OLT outcomes were similar between patients bridged or downstaged by TACE or Y90. A trend towards improved RFS for downstaged patients was identified.

1. Introduction

Orthotopic liver transplantation (OLT) is the standard of care for cirrhotic patients exhibiting unresectable hepatocellular carcinoma (HCC) within Milan criteria. This corresponds to United Network for Organ Sharing classification (UNOS) T2 disease [1–3]. For these patients, OLT is considered curative given similar overall survival (OS) compared to transplanted patients without HCC [2]. The major obstacle for successful transplantation is organ shortage. Hence, allocation schemas have been developed to prioritize organ recipients based on the severity of their illness. In case of HCC, patients who are being considered for OLT, should not progress beyond UNOS T2 stage (solitary lesion < 5 cm, 3 lesions all < 3 cm) or Milan criteria in order to maintain their HCC priority. Given this, liver-directed therapies

Abbreviations: OLT, orthotopic liver transplantation; TACE, transarterial chemoembolization; Y90, yttrium-90 radioembolization; HCC, hepatocellular carcinoma; LDT, liver directed therapy; UNOS, United Network for Organ Sharing classification; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic for Liver Cancer; CP, Child-Pugh score; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; MAA, macroaggregated albumin; MELD, model for end stage liver disease scoring system; MRI, magnetic resonance imaging; PVT, portal vein thrombosis; mRECIST, modified Response Evaluation Criteria in Solid Tumors; RFS, recurrence-free survival; RFA, radiofrequency ablation; US, ultrasound

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http://dx.doi.org/10.1016/j.ejrad.2017.05.022
Received 28 March 2017; Received in revised form 18 May 2017; Accepted 19 May 2017

(LDTs) have been applied for bridging HCC in order to minimize drop-out by preventing their progression. Another application of LDT is downstaging of UNOS T3 (solitary tumor > 5 cm, or 3 nodules with at least 1 > 3 cm) to T2 [4]. The EASL/EORTC clinical practice guidelines and international consensus conference recommend neoadjuvant LDT if the waiting list exceeds six months [5,6]. In its most recent guidelines update, the American Association for the study of Liver Diseases (AASLD), recommends bridging to transplant in patients listed for OLT within OPTN T2 (Milan) criteria to decrease progression of disease and subsequent dropout from the waiting list [7]. However, AASLD does not recommend one form of liver-directed therapy over another. Bridging LDTs include radiofrequency ablation, conventional TACE, drug eluting beads (DEB-TACE) and radioembolization (Y90) [8–11].

Over the last 10 years, our group has been active in analyzing the role of Y90 radioembolization in HCC. Following establishment of safety and standardization of technique, its role in bridging/downstaging to transplantation, portal vein thrombosis, neoadjuvant to resection (radiation lobectomy), radiation segmentectomy and comparative effectiveness has been described. Improved quality-of-life (compared with TACE) and the results of a randomized study of Y90 +/− sorafenib in the bridging setting were reported [12–20]. Most recently, the results of a randomized, phase 2 clinical trial comparing the outcomes of cTACE and Y90 radioembolization in patients with HCC, showed that Y90 resulted significantly time to progression to progression (TTP) (> 26 months) than TACE (6.8 months) ($p = 0.0012$) (hazard ratio, 0.122; 95% confidence interval [CI], 0.027–0.557; $p = .007$) [21].

In 2009, we reported outcomes post-OLT comparing Y90 and TACE [4]. Since then, we have continued to prospectively follow these patients. There are limited data on long-term outcomes of transplanted patients undergoing neoadjuvant bridging/downstaging with TACE or Y90. The purpose of our study was to study OS, recurrence free-survival (RFS), location of recurrence and factors predicting recurrence in transplanted patients following TACE or Y90 [22,23].

2. Methods

2.1. Study design

This study analyzed patients undergoing OLT for HCC following LDT with TACE or Y90 between January 2003 and April 2013 in a large, comprehensive transplant center with expertise in liver-directed interventional procedures. Data from our database included clinic visits, cross-sectional imaging, interventional and surgical procedures. The study was approved by the Institutional Review Board and was Health Insurance Portability and Accountability Act compliant.

2.2. Patient cohort and treatment group classification

Patients were included in this comprehensive analysis if they had been transplanted for HCC after treatment with TACE or Y90. Patients were classified in the TACE or Y90 group depending on the 1st LDT they received, irrespective of additional treatments received before OLT. Post LDT treatments were tabulated.

2.3. TACE and Y90

TACE and Y90 consisted of transcatheter intra-arterial injection of chemotherapeutic agents (30 mg mitomycin, 30 mg adriamycin and 100 mg cisplatin emulsified with lipiodol) or Y90ttrium-loaded glass microspheres (Therasphere, BTG, London, UK), respectively. Injections were performed in a lobar, segmental or subsegmental branch of the hepatic arterial vasculature, accordingly to previously published guidelines [24,25]. Y90 treatments were preceded by a simulation angiography with injection of ^{99m}Technetium-labeled macroaggregated albumin (MAA) to prevent extrahepatic deposition of Y90-loaded microspheres. Y90 patients were treated on an outpatient basis, while TACE patients were observed for 1–2 days as inpatients for management of post-embolization syndrome. Patients underwent follow-up imaging by contrast enhanced magnetic resonance imaging.

2.4. Baseline characteristics

Baseline data at 1st LDT included gender, etiology of liver disease, method of diagnosis, age, Child-Pugh score (CP), tumor distribution, multifocality of disease, UNOS stage, presence of portal vein thrombosis (PVT), BCLC stage and serum alpha-fetoprotein (AFP). The total number of LDTs (TACE, Y90, radiofrequency ablation) and combination or cross-over in therapies were reported. Immediate pre-transplant UNOS stage and AFP levels were recorded. AFP > 13 ng/mL was chosen as the cut-off value.

2.5. Transplant eligibility and post-transplant outcomes

OLT assignment was directed by the transplant team (Transplant surgery/Hepatology/Interventional Radiology) according to guidelines using the model for end stage liver disease scoring system (MELD) with upgrading points accorded to HCC patients within transplant criteria [26]. Following transplantation, patients underwent imaging follow-up per routine institutional guidelines, which included ultra-sonography and Doppler scanning for the transplanted liver at the time of discharge. Subsequently, we performed a q3 month imaging for the first year (if high risk) followed by 6 months thereafter for 3 years. If deemed necessary, CT chest was done at 6 months interval concurrently with other imaging. The date and site (intra/extrahepatic) of HCC recurrence, as well as the date of death were determined.

2.6. Statistical analyses

Baseline, treatment and pre-OLT characteristics were reported using descriptive methods (number for categorical variables, median and interquartile range [IQR] for continuous variables), and compared between groups using the Mann–Whitney (categorical) or Fisher's exact test (continuous variables). Downstaging ability of TACE and Y90 was reported using descriptive statistics (number/proportions) and McNemar test; AFP change was assessed by Wilcoxon test. RFS and OS were estimated from first LDT using Kaplan–Meier curves and uni/multivariate analysis of predicting factors of survival were performed using the Log rank test and the Cox proportional regression model by baseline pre-OLT characteristics.

3. Results

3.1. Treatment characteristics

172 patients were transplanted for HCC: TACE $N = 79$, Y90 $N = 93$. Baseline, treatment and pre-OLT characteristics are summarized in Table 1. Median age at first LDT was 60 years (IQR: 55–65 years), with HCV as the most frequent etiology (98/172, 57%). UNOS stage, Child–Pugh class, focality and AFP were comparable at first LDT. In the TACE group, significantly more LDT treatment sessions ($p = 0.0160$) were performed pre-OLT. There were ulterior treatments after first LDT: 1 patient in the TACE group received Y90; 1 Y90 patient received subsequent TACE. One Y90 (1%) and 8 (10%) TACE patients underwent RFA before OLT. One TACE patient was treated with sorafenib prior to the 1st TACE; 2 Y90 patients had undergone previous resection for HCC, one of them also being treated with sorafenib prior to Y90. Two patients in the Y90 group had undergone partial hepatic